isolated lissencephaly sequence

Isolated lissencephaly sequence (ILS) is a condition that affects brain development before birth. Normally, the cells that make up the exterior of the brain (cerebral cortex) are well-organized, multi-layered, and arranged into many folds and grooves (gyri). In people with ILS, the cells of the cerebral cortex are disorganized, and the brain surface is abnormally smooth with an absence (agyria) or reduction (pachygyria) of folds and grooves. In most cases, these abnormalities impair brain growth, causing the brain to be smaller than normal (microcephaly). This underdevelopment of the brain causes severe intellectual disability, delayed development, and recurrent seizures (epilepsy) in individuals with ILS.

More than 90 percent of individuals with ILS develop epilepsy, often within the first year of life. Up to 80 percent of infants with ILS have a type of seizure called infantile spasms, these seizures can be severe enough to cause brain dysfunction (epileptic encephalopathy). After the first months of life, most children with ILS develop a variety of seizure types, including persisting infantile spasms, short periods of loss of consciousness (absence seizures); sudden episodes of weak muscle tone (drop attacks); rapid, uncontrolled muscle jerks (myoclonic seizures); and episodes of muscle rigidity, convulsions, and loss of consciousness (tonic-clonic seizures).

Infants with ILS may have poor muscle tone (hypotonia) and difficulty feeding, which leads to poor growth overall. Hypotonia also affects the muscles used for breathing, which often causes breathing problems that can lead to a life-threatening bacterial lung infection known as aspiration pneumonia. Children with ILS often develop muscle stiffness (spasticity) in their arms and legs and an abnormal side-to-side curvature of the spine (scoliosis). Rarely, the muscle stiffness will progress to paralysis (spastic paraplegia). Individuals with ILS cannot walk and rarely crawl. Most children with ILS do not develop communication skills.

Frequency

ILS affects approximately 1 in 100,000 newborns.

Genetic Changes

Mutations in the *PAFAH1B1*, *DCX*, or *TUBA1A* gene can cause ILS. *PAFAH1B1* gene mutations are responsible for over half of ILS cases; *DCX* gene mutations cause about 10 percent of cases; and *TUBA1A* gene mutations cause a small percentage of ILS. These genes provide instructions for making proteins that are involved in the movement (migration) of nerve cells (neurons) to their proper locations in the developing brain. Neuronal migration is dependent on cell structures called microtubules. Microtubules

are rigid, hollow fibers that make up the cell's structural framework (the cytoskeleton). Microtubules form scaffolding within the cell that elongates in a specific direction, altering the cytoskeleton and moving the neuron. The protein produced from the *TUBA1A* gene is a component of microtubules. The proteins produced from the *DCX* and *PAFAH1B1* genes promote neuronal migration by interacting with microtubules.

Mutations in any of these three genes impair the function of microtubules and the normal migration of neurons during fetal development. As a result, the layers of the cerebral cortex are disorganized and the normal folds and grooves of the brain do not form. This impairment of brain development leads to the smooth brain appearance and the resulting neurological problems characteristic of ILS.

Some individuals with ILS do not have an identified mutation in any of these three genes; the cause of the condition in these individuals may be unidentified mutations in other genes that affect neuronal migration or other unknown factors.

Inheritance Pattern

The inheritance pattern of ILS depends on the gene involved.

When ILS is caused by mutations in the *PAFAH1B1* or *TUBA1A* gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

When mutations in the *DCX* gene cause ILS, it is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the *DCX* gene in each cell is sufficient to cause the condition. In females, who have two copies of the X chromosome, one altered copy of the *DCX* gene in each cell can lead to a less severe condition in females called subcortical band heterotopia, or may cause no symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- classical lissencephaly
- ILS
- LIS1
- lissencephaly type 1
- lissencephaly, classic
- type 1 lissencephaly

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Lissencephaly 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1843916/
- Genetic Testing Registry: Lissencephaly 3
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1969029/
- Genetic Testing Registry: Lissencephaly, X-linked
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848199/

Other Diagnosis and Management Resources

- GeneReview: DCX-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1185
- GeneReview: LIS1-Associated Lissencephaly/Subcortical Band Heterotopia
  https://www.ncbi.nlm.nih.gov/books/NBK5189
- GeneReview: Tubulinopathies Overview
  https://www.ncbi.nlm.nih.gov/books/NBK350554

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Brain Malformations
  https://medlineplus.gov/brainmalformations.html
- Health Topic: Epilepsy
  https://medlineplus.gov/epilepsy.html

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page
- National Institute of Neurological Disorders and Stroke: Lissencephaly Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Lissencephaly-Information-Page

Educational Resources

- Cleveland Clinic
  http://my.clevelandclinic.org/health/articles/lissencephaly
- Disease InfoSearch: Lissencephaly 1
  http://www.diseaseinfosearch.org/Lissencephaly+1/4269
- Kennedy Krieger Institute: Brain Malformations
  https://www.kennedykrieger.org/patient-care/diagnoses-disorders/brain-malformations
- MalaCards: lis1-associated lissencephaly/subcortical band heterotopia
  http://www.malacards.org/card/lis1_associated_lissencephaly_subcortical_band_heterotopia
- Orphanet: Lissencephaly
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=48471

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
  http://aaidd.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/lissencephaly/
- Resource List from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/lissence.html

GeneReviews

- DCX-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1185
- LIS1-Associated Lissencephaly/Subcortical Band Heterotopia
  https://www.ncbi.nlm.nih.gov/books/NBK5189
- Tubulinopathies Overview
  https://www.ncbi.nlm.nih.gov/books/NBK350554

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22type+1+lissencephaly%22+OR+%22Classical+Lissencephalies+and+Subcortical+Band+Heterotopias%22+OR+%22Lissencephaly%22+OR+%22Neuronal+Migration+Disorders%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28isolated+lissencephaly+sequence%5BTIAB%5D%29+OR+%28classical+lissencephaly%5BTIAB%5D%29+OR+%28classic+lissencephaly%5BTIAB%5D%29+OR+%28type+1+lissencephaly%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- LISSENCEPHALY 1
  http://omim.org/entry/607432
- LISSENCEPHALY 3
  http://omim.org/entry/611603
- LISSENCEPHALY, X-LINKED, 1
  http://omim.org/entry/300067

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